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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,104	02/04/2002	Jeffery A. Bluestone	TOLT:006USD4	5806

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,104	BLUESTONE, JEFFERY A.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/4/02, 11/13/03 and 6/4/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *3,4,6,9-15,20 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7,8,16-19,21-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *filed* 11/13/03 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendments filed 2/4/02 (Paper No. 1.5) and 11/13/02 (Paper No. 6) and Applicant's response filed 6/4/03 (Paper No. 9) are acknowledged and have been entered.

2. Applicant's election without traverse of the species OKT3 as the immunopotentiating protein and a tumor-specific or tumor-associated antigen as the second compound having an epitope in Paper No. 6 is acknowledged.

Claims 1, 2, 5, 7, 8, 16-18 and 26-29 read on the elected species. Note that "microorganism" recited in instant claim 2 encompasses viruses.

Upon consideration of the prior art, the search has been extended to include the species of viral specific or associated epitope, and hepatitis surface antigen and HIV env-associated antigen gp120 T1 or T2.

Accordingly, claims 3, 4, 6, 9-15 and 20 and 25 (non-elected species) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 2, 5, 7, 8, 16-19, 21-24 and 26-29 are currently being examined.

4. The disclosure is objected to because of the following informalities:

(1) the abstract of the disclosure has spelling errors at line 2 "response" and line 3 "eleicit".

(2) In the Brief Description of the Drawings: Figure 1 should be Figure 1 A-C, Figure 2 should be Figure 2 A-1-B-4, Figure 4 should be Figure 4A-B, Figure 5 should be Figure 5A-B, Figure 8 should be Figure 8 A-D, Figure 10 should be Figure 10A-1-B-3, Figure 16 should be Figure 16A-B.

Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 5, 16-19, 21-24 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed immunopotentiating composition comprising an immunopotentiating protein and a second compound having an epitope against which a cellular or humoral immune response is required, including those recited in the instant claims.

The instant claims encompass an immunopotentiating protein which is any agent of undisclosed structure, other than being a protein, which may affect the immune response at a variety of different levels or upon a variety of different cell types, including T cells.

The specification discloses that immunopotentiation includes both activation and potentiation (page 12 at lines 15-17) and that immunopotentiation may include cell proliferation, increased DNA synthesis, increased production of cytokines, increased production of cytotoxic cells, calcium efflux or any other change that raises the cell above the basal or resting state (page 12 at lines 4-14). The specification discloses antibodies against TCR associated CD3 chains, such as anti-CD3, antibodies against T cell surface antigens CD2, CD28, Thy-1 and Ly-6, and SEB as immunopotentiating proteins (page 14 at lines 4-28). The specification further discloses use of immunopotentiating agents in immunogen compositions such as vaccines, where the agents serve as "adjuvants" (page 15 at lines 6-19).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "immunopotentiating protein", is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of activating or potentiating the immune response. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than that they comprise proteins. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a

definition by function does not suffice to define the genus because it is only an indication of what the property the protein has, and if one extends the analysis in the instant case, what the protein does, rather than what it is. See Fiers, 84 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

7. Claims 1, 2, 5, 16-19, 21-24 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunopotentiating composition comprising an immunopotentiating protein which is an anti-CD3 antibody or antibody to T cell surface antigens CD2, CD28, Thy-1 and Ly-6 or SEB, and a second compound having an epitope against which a cellular or humoral immune response is required, does not reasonably provide enablement for an immunopotentiating composition comprising an immunopotentiating protein and a second compound having an epitope against which a cellular or humoral immune response is required. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass an immunopotentiating protein which is a protein of undisclosed structure which may affect the immune response at a variety of different levels or upon a variety of different cell types, including T cells.

The specification discloses that immunopotentiation includes both activation and potentiation (page 12 at lines 15-17) and that immunopotentiation may include cell proliferation, increased DNA synthesis, increased production of cytokines, increased production of cytotoxic cells, calcium efflux or any other change that raises the cell above the basal or resting state (page 12 at lines 4-14). The specification discloses antibodies against TCR associated CD3 chains, such as anti-CD3, antibodies against T cell surface antigens CD2, CD28, Thy-1 and Ly-6, and SEB as immunopotentiating proteins (page 14 at lines 4-28). The specification further discloses use of immunopotentiating agents in immunogen compositions such as vaccines, where the agents serve as "adjuvants" (page 15 at lines 6-19).

Evidentiary reference Ellenhorn et al (Science 1988 242, 569-571, IDS reference C39) teaches that low dose administration of anti-CD3 mAb prevents malignant progressor tumor growth, but at administration at high concentrations, results in suppression of T cell function (especially pages 569).

Undue experimentation would be required. The enablement provided by the specification is not commensurate with the scope of the claims. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 16-19, 21-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-19 and 26 recite the limitation "second protein". There is insufficient antecedent basis for this limitation in the claims.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 5, 7, 16-18, 27 and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Bluestone et al (IDS reference C19, 11/1988).

Bluestone et al teach injection of mice with a mixture of anti-CD3 and fragments of a tumor variant. Claims 16-18, 27 and 28 are included in the instant rejection because the fragments contain peptides and proteins which comprise tumor specific epitopes.

12. Claims 1, 2, 16, 17, 19, 21, 24 and 26-29 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 4,772,547.

US Patent No. 4,772,547 discloses vaccine compositions comprising antigenic peptides or proteins from hepatitis surface antigen and HIV envelope and adjuvants such as IFN, IL-2, thymosin alpha 1 (i.e., immunopotentiating proteins) (especially column 8 at lines 25-49). US Patent No. 4,772,547 further discloses enhancing immunogenicity of the peptides by coupling the peptides covalently (via Cys, i.e., by "crosslinking") to toxoids or carrier materials that enhance immunogenicity. Claim 26 is included in the instant rejection because the instant specification discloses conjugation being in the nature of a chemical or molecular crosslink (page 15 at lines 25-30).

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 5, 7, 8, 16-18, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bluestone et al (IDS reference C19, 11/1988) in view of Mezzanzanica et al (Int. J. Cancer, 41, 609-615, 1988).

Bluestone et al teach injection of mice with a mixture of anti-CD3 and fragments of a tumor variant.

Bluestone et al do not teach that the anti-CD3 antibody is OKT3.

Mezzanzanica et al teach anti-CD3 mAb OKT3 and a defined target antigen on human ovarian carcinoma cells and an antibody against the said antigen (especially page 609, column 2, MAbs section). Mezzanzanica et al further teach antibodies comprising anti-CD3 antibodies administered in humans to induce T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a composition like that taught by Bluestone et al for use in a human comprising the OKT3 antibody taught by Mezzanzanica et al and a target antigen.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a composition to treat human ovarian tumors as taught by Mezzanzanica et al and because Bluestone et al teach low dose administration of anti-CD3 and fragments of a tumor to produce anti-tumor immunity and prevents malignant tumor growth. Claims 16-18, 27 and 28 are included in the instant rejection because the tumor cell fragments

taught by Bluestone et al contain peptides and proteins which comprise tumor specific epitopes and the target antigen taught by Mezzanzanica et al comprises a tumor specific epitope(s).

15. Claims 19, 21-24, 26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,772,547 in view of Bluestone et al (IDS reference C19) and Mezzanzanica et al (Int. J. Cancer, 41, 609-615, 1988) as applied to claims 1, 5, 7, 8, 16-18, 27 and 28 and further in view of EP 0273716 A2.

US Patent No. 4,772,547 discloses vaccine compositions comprising antigenic peptides and proteins from hepatitis surface antigens and HIV envelope and adjuvants such as IFN, IL-2, thymosin alpha 1 (especially column 8 at lines 25-49). US Patent No. 4,772,547 further discloses enhancing immunogenicity of the peptides by coupling the peptides covalently (via Cys, i.e., by "crosslinking") to toxoids or carrier materials that enhance immunogenicity. Claim 26 is included in the instant rejection because the instant specification discloses conjugation being in the nature of a chemical or molecular crosslink (page 15 at lines 25-30).

US Patent No. 4,772,547 does not disclose an immunopotentiating composition comprising an imunopotentiating protein that is anti-CD3 and a second compound having an epitope against which a cellular or humoral immune response is desired.

Bluestone et al teach injection of mice with a mixture of anti-CD3 and fragments of a tumor variant.

Mezzanzanica et al teach anti-CD3 mAb OKT3 and a defined target antigen on human ovarian carcinoma cells and an antibody against the said antigen (especially page 609, column 2, MAbs section). Mezzanzanica et al further teach antibodies comprising anti-CD3 antibodies administered in humans to induce T cells.

EP 0273716 A2 teaches HIV gp120 envelope protein antigen of HIV and T1 and T2 antigenic peptides and treatment of HIV (especially page 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a composition like that taught by Bluestone et al for use in a human comprising the OKT3 antibody taught by Mezzanzanica et al and a target antigen such as the antigens taught by EP 0273716 A2 for the treatment of HIV and to have coupled the anti-CD3 enhancer of immunogenicity to the antigen as disclosed by US Patent No. 4,772,547 in the vaccine compositions disclosed by US Patent No. 4,772,547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat HIV as taught by EP 0273716 A2 using HIV antigenic peptides taught by EP 0273716 A2 and because Bluestone et al teach administration of anti-CD3 and fragments of a tumor to produce immunity to the target antigen, Mezzanzanica et al teach use of OKT3 in humans and US Patent No. 4,772,547 discloses vaccines comprising antigens coupled to materials that enhance immunogenicity.

16. The references crossed out in the Form 1449 filed 11/13/02 have not been considered because they can' be located in the parent application Serial No.08/459,486. They will be considered in the next Office Action. It would expedite prosecution if Applicant would send in copies of references.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Marianne DiBrino, Ph.D.
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Group 1640
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October 30, 2003

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